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Evaluation of persistent pulmonary hypertension of the newborn (PPHN) in Upper Egypt☆

Persistent Pulmonary hypertension of the newborn (PPHN) occurs in 1.9 per 1000 live births, but a wide variation in the incidence (0.43–6.82 per 1000 live births) has been reported between centers.

Persistent pulmonary hypertension of the newborn is a complex disorder that is associated with a wide array of cardiopulmonary diseases and is characterized by marked pulmonary hypertension and altered vasoreactivity, leading to the right-to-left shunting of blood across the patent ductus arteriosus and/or foramen ovale.

PPHN is a potentially fatal complication of the circulatory maladaptation. It leads to profound hypoxemia secondary to right-to-left shunting across the foramen ovale and/or ductus arteriosus as a result of increased pulmonary venous return (PVR).

Treatment of PPHN aims at maximizing pulmonary blood flow and minimizing PVR without compromising cardiac output. A range of therapeutic options are available for the management of PPHN including: extracorporeal membrane oxygenation (ECMO), high frequency ventilation (HFV), surfactant and inhaled nitric oxide (iNO). The high cost of these technically demanding modalities is the main concern for developing countries. Inability to provide and maintain the required training and expertise is also an issue.

1. Aim of the study

To Assess The Magnitude of The Problem, Risk Factors, Clinical Profile, Some Available Therapeutic Modalities and Outcome of PPH.

2. Patient and methods

2.1. Design:

A random, cross sectional observational, prospective study.
Period: from 1st June 2008 to the end of June 2010.
Place of study: Neonatal intensive Care Units (NICU) at Sohag & Assiut University Hospitals.
Patients: 54 Newborns.

2.2. Inclusion criteria:

1) >37 weeks' gestation,
2) Absence of structural congenital heart diseases,
3) Admitted to the NICU between June 1, 2008 and 30 June 2010.

2.3. Exclusion criteria:

1) Cardiac arrest or terminal disease (arterial pH <6.80, bradycardia <90 beats/minute or unrecordable blood pressure),
2) Preterm babies,
3) CNS cause of cyanosis.

2.4. Diagnosis of PPHN is based on:

Tachypnea, tachycardia, respiratory distress, central cyanosis, heart murmur or abnormal heart sounds, echocardiography and blood gas differences.

2.5. Right-to-left shunting is evidenced by:

A discrepancy in the pre- and post-ductal saturations; a Pa02 difference of at least 20 between the pre (right radial) and post (umbilical) ductal arterial blood sample.

Or pulse oximetry findings of preductal (right finger) oxygen saturation (Sa02) exceed post-ductal (toe) Sa02 by ~5%.

Echocardiography demonstrates the absence of congenital heart diseases and presence of right to left shunts through patent foramen ovale and for patent ductus arteriosus.

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2.6. All neonates in the study were subjected to:

- Full antenatal and postnatal histories,
- Full clinical examination,
- Serum glucose, calcium, hematocrit, WBC with differential, platelet count, serum electrolytes, lumbar puncture and blood cultures (if suspected septicemia),
- Pulse oximetry: for transcutaneous oxygen estimations of preductal (right finger), postductal (right toe),
- Serial arterial blood gases,
- Chest X-ray,
- Cranial ultrasound of the head (in some selected brain insult),
- Electrocardiogram,
- Echocardiogram,
- Continuous monitoring of oxygenation, blood pressure, and perfusion.

2.7. Medications & protocols for administration:

- Pancuronium (pavulon):*if baby needs mechanical ventilations:* In a dose of 0.05–0.15 mg/kg/dose IV bolus q1–2 h, alternatively, 0.01–0.1 mg/kg/h IV continuous infusion.
- Dopamine: *if baby hypotenuse (shocked):* continuous infusion:2–20 mcg/kg/min IV.
- Dobutamine (Dobutrex): if *baby hypotenuse (shocked)*:In 2–20 mcg/kg/min IV Sodium bicarbonate: Slow bolus infusion: 2–3 mEq/kg IV for neonates with acidosis and guided by improvement of arterial blood gases.
- Sodium bicarbonate: Slow bolus infusion: 2–3 mEq/kg IV for neonates with acidosis and guided by improvement of arterial blood gases.
- **Oral Sildenafil citrate: given as follows:**

~ The solution for sildenafil was prepared by crushing a 50 mg tablet of sildenafil in Orabase (diluents) to make a concentration of 2 mg/ml.
~ *The protocol for dosing was*
~ first dose of 1 mg/kg (0.5 ml/kg) within 30 min after admission to NICU,
~ Dosing every 6 h,
~ Dose could be doubled (1 ml/kg) if the oxygenation did not improve and blood pressure remained unstable, and
~ The treatment was discontinued if there was no significant change in oxygenation after 36 h, or patient has received eight doses. This strategy had been subjected to many previous controlled trial evaluations.

- **Magnesium sulfate:**

~ A loading dose of *250 mg/kg* of magnesium sulfate IV over 10–15 min.
~ If a clinical response is obtained once the serum magnesium level exceeds 3,5 mmollL given between 20 and 7-5 mg/kg for 2–5 days, while maintaining a blood level of between 3–5 and 5,5 mmol/L.[10–12]

2.8. Mechanical ventilation:

Used in neonates with

1. Extreme acidosis (pH < 7.1 0),
2. Resistance to treatment,
3. Severe neonatal pneumonia,
4. Massive lung collapse, and
5. Severe parenchymal lung diseases.

2.9. Follow up:

For the first six months, it included evaluation for CNS injury by performing complete neurological examination by pediatric neurologist and in some of them by doing cranial sonograms, EEG, brain CT and/or MRI hearing test & fundus examination.

2.10. A consent had been taken from parents

The study had been approved from scientific ethics committee of Sohag & Assiut University Hospitals.

3. Results

Table 1. Demographic data of studied neonates.

Variable	No.	%
Gestational age (weeks)		
Full term	42	77.8
Post-term	12	22.2
Birth weight (kg)		
Appropriate for date	34	62.9
Large for date	12	22.2
Small for date	8	14.8
Gender		
Boys	31	57.4
Girls	23	42.6
Mode of delivery		
Vaginal	19	35.2
LSCS	27	50.0
USCS	8	14.8
Age of presentations		
At birth	6	11.1
2–3 days after birth	24	44.4
3–5 days after birth	16	29.7
> 5 days after birth	8	14.8
Hospital delivery	42	77.8
Home delivery	12	22.2

Table 2. Clinical profile of neonates with PPHN.

Clinical parameters	No.	%
Respiratory distress(RDS)	54	100
Mild	7	12.9
Moderate	30	55.5
Severe	17	31.5
Fast heart rate	46	85.1
Cyanosis	46	85.1
Acidosis	15	27.8
Cardiomegaly	21	38.8
Loud S2	48	88.9
Murmurs (TR)	36	66.7
Hepatomegaly	21	38.9
Hypotension	18	33.3
Hypothermia	5	9.3
Hypoglycemia	11	20.4
Hypocalcaemia	6	11.1

Table 3. Etiological (possible detected risk factors) for PPHN.

Variable	No.	%
Fetal factors		
Meconium aspiration syndrome (MAS)	19	35.2
Birth asphyxia	10	18.5
Hyaline membrane diseases (HMD)	8	14.8
Infant of diabetic mother(IDM)	7	12.9
Transient tachypnea of newborn	3	5.6
Neonatal pneumonia	6	11.1
Postdate (>40 weeks)	2	3.7
Diaphragmatic Hernia	2	3.7
Lung hypoplesia	1	1.9
Down syndrome	5	9.3
Proven neonatal septicemia	7	12.9
Maternal diseases		
Maternal IDM	14	25.9
Maternal hypertension	8	14.8
Maternal anemia	3	5.6
Idiopathic (black lung or clear lung) PPHT	6	14.8

4. Discussion

PPHN represented nearly 3% (541/1801 cases) of total neonatal care unit admissions and 11% (54/486 cases) of NICU admission and it was considered the sixth leading cause of death in our nursery units in year 2009.

Meconium stained, birth asphyxia, hyaline membrane diseases, neonatal septicemia, post-term birth, large for gestational age, cesarean section, maternal diabetes mellitus were associated with an elevated risk for PPHN.

Table 4. Comparison of rate of improvement due to oral sildenafil and magnesium sulfate.

Variable	No.	%
Improved	24	44.4
Chronic lung diseases	4	7.4
Neurodevelopment impairment	10	18.5
Missed follow up	4	7.5
Expired	12	22.2

The majority of neonates were delivered by CS due to prenatal problems.

Numerous publications have reported cesarean section delivery, including elective cesarean delivery, to be associated with a high incidence of respiratory distress syndrome and PPHN.

Cesarean section itself might cause PPHN or might be attributed to underlying fetal conditions that triggered the intervention and ultimately results in PPHN.

Home delivery carries also a risk for PPHN in those neonates and 90% of neonates proved to have septicemia with PPHN were home delivered.

Home delivery in our locality is usually performed by non expert personnel in unclean, unhygienic conditions and usually associated with high incidence of neonatal infections which may lead to occurrence of pulmonary hypertension.

Sildenafil citrate promotes selective smooth muscle relaxation in lung vasculature possibly by inhibiting phosphodiesterase type 5 (PDE5). This results in subsequent reduction of blood pressure in pulmonary arteries and increase in cardiac output.

Oral sildenafil was administered easily and was tolerated and improved oxygenation index in infants with severe PPHN.

So it may be a useful adjuvant therapy for term infants with pulmonary hypertension in centers lacking inhaled nitric oxide and extracorporeal membrane oxygenation.

Intravenous magnesium sulfate (MgS04) has been used extensively in developing countries for the treatment of PPHN.

It is cheap and easily available, and has a potential neuroprotective effect. Its main disadvantage is that it can cause systemic hypotension.

The mortality & morbidity rates in our neonates were higher than those reported in some previous studies and may be attributed to late presentation, delayed diagnosis and unavailability of other highly effective therapeutic modalities like inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO) and more recently vasodilators agents like tolazoline.

5. Conclusion

Meconium stained, birth asphyxia, hyaline membrane diseases, neonatal septicemia, post-term birth being large for gestational age, cesarean section, maternal overweight and diabetes mellitus were associated with an elevated risk for PPHN.

Further reading

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